REMARKS

Claims 44-49, 51-53, 63, 70-79, 83 and 84 are pending in the application. Claims 1-43, 50, 55-57, 62, 65 and 81-82 were cancelled in a prior Amendment and claims 54, 58-61, and 64-69 are cancelled by this Amendment. The claims have been amended to omit the descriptor "synthetic" from the claims. Claims 1 and 63 have been amended to recite the specific types of differentiation-promoting factors for use in contacting the progenitor cells. Support for this Amendment is found at page 6 of the Specification.

I. Objection to Claim 52 - Improper Dependent Form.

At item 2 of Paper No. 16, the Examiner maintains the rejection of claim 52 under 37 C.F.R. 1.75(c) as being of improper dependent form for failing to further limit the subject matter of the previous claim. Applicants continue to traverse this rejection.

Claim 52 is directed to the neuronal tissue of claim 44 wherein such tissue is derived from a single cell. Claim 44 is directed to a neuronal tissue that is derived from a brain or spinal cord **tissue**. As is known to a person of skill in the art, a "tissue" is a collection of single cells, *see* Oxford Dictionary of Biochemistry and Molecular Biology (1997) at 649, attached hereto, and a population of cells may be culture from a single cell or from a collection of cells.

Thus, claim 52 does limit claim 44, as it is drawn to neuronal tissues derived from a single cell of a brain or spinal cord tissue (collection of cells). The Examiner himself makes this point in the Office Action when he states that a brain or spinal cord tissue comprises many types of cells. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the objection.

II. Rejection Under 35 U.S.C. § 112, First Paragraph - Written Description.

The Examiner has maintained the rejection of claims 44-49, 51-54, 58-61, 63-64, 66-79 and 83-84 under 35 U.S.C. § 112, first paragraph, asserting that these claims contain subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the invention. As basis for the maintenance of these rejections, the Examiner provides scant

information, relying instead on the reasons made of record for claims 26-43 in Paper Nos. 9 and 12. The applicants traverse this rejection.

First, as a threshold matter, the applicants submit that this rejection is not proper, as the Examiner has failed to explain why, with respect to each of the twelve points, the Examiner does not find the applicant's arguments presented in the prior response persuasive. Accordingly, the applicant submits that this is not a proper Office Action, and requests that in the next communication, if such rejection is maintained, that the Examiner provide precise and explicit reasons why each of the applicant's assertions is deemed to be unpersuasive.

With respect to the specific substantive rejections, as discussed in the prior response, the Examiner argues that there is no written support in the Specification for the following:

(i) "synthetic neuronal tissue,"

(ii) "partially differentiated neuronal progenitor cells that maintain their capability to perform mitosis,"

(iii) ". . . differentiation-promoting factor are contacted for at least two hours,"

(iv) "separated . . . after at least two hours,"

(v) "wherein the factor is an extra cellular matrix of human tissue,"

(vi) "wherein the recipient and the mammal are the same individual,"

(vii) "wherein the single progenitor cell is selected on the basis that it expresses a marker characteristic of the selected type of neuron,"

(viii) "the single neuronal progenitor cell is proliferated by contacting the cell with a mitogen after selecting the cell,"

(ix) "wherein the synthetic tissue does not comprise sufficient glial cells to provoke an immune response . . . recipient,"

(x) "<90% [95%] of cells in the synthetic tissue are the progenitor cells,"

(xi) "partial differentiation is performed more than once," and

(xii) "proliferating the sub-cloned partially-differentiated neuronal progenitor cell." The applicant respectfully traverses these rejections.

With respect to the terms designated items nos. i, iii, iv, v, vi, and vii it is believed that the § 112 rejection is no longer applicable as the claims containing these phrases are cancelled, either in this Amendment or the prior Amendment. Accordingly, the Examiner's express withdrawal of these rejections is requested.

None of the remaining subject matters listed above is new matter under § 112, first paragraph. As discussed in the prior response, there is no *in hac verba* requirement when evaluating written description; it is sufficient that the elements of the claims are supported implicitly or inherently by the Specification. M.P.E.P. 2163.

With respect to the phrase "partially differentiated neuronal progenitor cells that maintain their capability to perform mitosis" (item ii), support is found in the Specification at page 3, lines 12-14, 17-19. ("tissue ... is prepared according to the invention which includes ... partial differentiation *in vitro*.";). Using the Specification as information to be coupled with the knowledge charged to a person of skill in the art, this person would have understood that partially differentiating cells are those which have descended sufficiently far on the differentiation pathway such that they are no longer totipotent, but have not entered into the phrase of terminal differentiation, and as such, remain capable of differentiating into "species" of neuronal tissue cells, such as dopaminergic neurons. *See also* pages 5-7 of the Specification (describing partial differentiation of neuronal progenitor cells that maintain their ability to mitose).

With respect to the phrase "the single neuronal progenitor cell is proliferated by contacting the cell with the mitogen after selecting the cell" (item VIII), support is found in the Specification at page 9, lines 23-34 to page 10, lines 1-25. In that portion of the Specification, an example is provided in which fetal and adult progenitor cell cultures are expanded (proliferated) by culturing the cells in the presence of mitogens ("supplemented with sufficient concentrations of mitogen;" "the expansion medium may contain mitogens").

The Examiner argues that those portions of the claims reciting "wherein the synthetic tissue does not comprise sufficient glial cells to provoke an immune response ... recipient" (item IX) is not supported in the Specification. In fact, the contrary is correct. The Specification, at page 2, lines 3-12, explains that the cultures (the inventive tissues) do not include cells that give

rise to immunogenic glial cells in large enough quantities to induce any detectable immune response.

The Examiner argues that this phrase "is not the same" as cultures that do not include cells that give rise to immunogenic glial cells in large enough quantities to induce any detectable immune response. First, as is clear from a reading of the entire Specification, the applicant has used "culture" throughout to express the population of cells that is the neuronal tissue of the claims. Second, applicant has amended the claims to recite that the neuronal tissue does not comprise sufficient cells that give rise to glial cells to provoke an immune response.

With respect to the phrase "less than 90% [95%] of the cells in the synthetic tissue are the progenitor cells," no such phrase is found in the claims. The claims do recite a neuronal tissue wherein more than 95% of the cells in the tissue are the progenitor cells, but such claim element is fully supported in the Specification at least at page 2, lines 17-18. ("greater than 90%, preferably greater than 95%".)

Finally, the Examiner has maintained the rejection of the claims based upon the lack of written description for the language "partial differentiation is performed more than once" and "proliferating the subcloned partially differentiated neuronal progenitor cell." Support for each of these phrases is provided expressly in the Specification. The "partial differentiation" language is supported at least at page 5, lines 2-16.

For at least these reasons, it is respectfully requested that the Examiner reconsider and withdraw the 35 U.S.C. § 112, first paragraph rejections.

III. Rejection Under 35 U.S.C. § 112, Second Paragraph - Indefiniteness.

The Examiner has maintained the rejection of claims 44-49, 51-54, 58-61, 63-64, 66-79 and 83-84 under 35 U.S.C. § 112, second paragraph, asserting that these claims are indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically, it appears that the Examiner believes that the term "differentiation-promoting factor" is indefinite. The claims have been amended to recite the specific differentiation-promoting factors for use in the composition and process of the invention. Accordingly, the Examiner's rejection is no longer applicable. Its reconsideration and withdrawal is respectfully requested.

IV. Rejections Under 35 U.S.C. § 102(b) Based Upon U.S. Patent No. 5,411,883 and International Patent Application Publication No. WO 97/02049.

The Examiner has maintained the rejection of claims 44-49, 51-54, and 58-84 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,411,883 of Boss, *et al.* ("Boss") and International Patent Application Publication No. WO 97/02049 of Luskin ("Luskin"), each taken individually.

The Examiner contends that Boss teaches isolation of human and porcine neuron progenitor cells that are "brain-derived neuronal tissue" from the mesencephalon. The Examiner asserts that these cells inherently contain progeny of a single totipotent neuronal stem cell derived from immature progenitor cells. The Examiner has rejected the applicant's previous arguments, asserting that "no purity limitations etc." are recited in the claims to distinguish them from Boss.

With respect to Luskin, the Examiner has previously asserted that Luskin teaches isolation of human and mammalian brain-derived neuronal progenitor cells capable of differentiating into more than 90% dopaminergic neurons. According to the Examiner, Luskin's progenitor cells contain less than 5%, and even less than 2% glial cells. The Examiner states that "immature progenitor cells" are inherently the progeny of single multi-potent neuronal stem cells. Again, the Examiner argues that applicant's prior arguments are non-persuasive as the claims recite "no purity limitations etc."

The applicant respectfully traverses each of these rejections.

Neither Boss nor Luskin anticipates the claimed invention, for neither reference teaches every element of the invention. Specifically, neither teaches partially differentiated neural progenitor cells that maintain their capacity to perform mitosis and are capable of differentiating into substantially only dopaminergic neurons upon contact of the neuronal tissue with a differentiation promoting factor as recited in the claims.

In support of this contention, the applicants submit herewith the Declaration of Johannes Schwarz (hereinafter "Dec."). The Declaration provides evidence that neither Boss nor Luskin teaches a neuronal tissue that is made of partially differentiated neuronal progenitor cells that maintain the capacity to perform mitosis and differentiate substantially into dopaminergic

neurons upon contact with specific factors, and yet do not include a population of glial cells of sufficient number to provoke an immunity response when implanted into a recipient.

The Boss Reference

Boss teaches that cell culture methods for the proliferation of "neuronal progenitor cells" *in vitro*, or for the terminal differentiation of those neuronal progenitor cells into dopamine-producing cells *in vitro* or post implantation. Col. 3, ll. 35-43. The neuronal progenitor cells described in Boss are obtained from the dopaminergic system of the brain, from an area which, *in vivo*, differentiates into a relatively high concentration of TH-positive neurons. Col. 5, ll. 25-30. The cell cultures of the Boss invention have a "loci of undifferentiating cells and loci of neurons." Col. 5, l. 53. Moreover, at least with respect to the monolayer cultures of the Boss invention, Boss teaches that among the cells which differentiate into neurons, glial cells may also be observed. Col. 6, ll. 10-13.

Boss also teaches that the neuronal progenitor cells of Boss may be induced to terminal differentiation into neurons by use of a differentiation agent that is sodium butyrate, butyric acid, cAMP derivatives, phosphodiestarase inhibitors, adenylate cyclase activators, and prostaglandins. Col. 13, ll. 35-50. Boss reports that upon completion of *in vitro* differentiation, the cell cultures contain "differentiated progenitor cells" that are no longer mitotic. Col. 13, ll. 66-68. Moreover, a person of skill would know that the undifferentiated cell cultures of Boss are capable of differentiating into a variety of cells, such as glial cells, not solely dopaminergic neurons. Dec. at ¶ 9. In Col. 12 of Boss, the passaging of neural epithelial cells is described. Under item 12, selection of specific cells using FACS or MACS is disclosed. Col. 12, ll. 53-63. Boss asserts "following growth of the neuron progenitor cell cultures for five to fifteen days, the cultures can be implanted." However, the cell selection protocol would not give rise to cells that would differentiate substantially into only dopaminergic neurons; rather, the selected cells would still possess some capability of differentiating into at least more than one type of cell, including glial cells. Dec. at ¶ 9. Boss teaches only a cell culture method that includes development of a cell culture containing undifferentiated neural progenitor cells into a cell culture that contains either a large population of undifferentiated neural progenitor cells or a cell culture that contains undifferentiated neural progenitor cells and terminally differentiated dopamine producing cells.

The Luskin Reference

Luskin teaches a composition that is about 95% mammalian, non-tumor-derived neuronal progenitor cells that express a neuron specific marker and which can give rise to progeny that can differentiate into neuronal cells. Luskin discloses that these neuronal cells are to be derived from the anterior sub-ventricular zone of the rat brain. Page 7 at ll. 22-23. All of the examples given in Luskin relate to the isolation, proliferation, differentiation, genetic modification, and transplantation of this type of rat cells. Luskin teaches that the cells can be cultured and expanded, that they are capable of dividing *in vivo* after transplantation, and that the Luskin composition is a source of dividing cells having the characteristics of neuronal cells. Page 12, ll. 12-13; page 12, ll. 15-16; page 13, ll. 8-10; page 16, ll. 13-15.

Example 3 describes the culturing of cells and their differentiation after plating. Since however the cells have not been differentiated, they are not determined and they therefore would not differentiate into a mixture of types of neuronal cells, *i.e.*, dopaminergic neurons, gabaergic, cholinerginic, etc. after transplantation. Thus, while each of these cell types is a neuron or a neuronal cell, there can be no dispute that the compositions of Luskin are not substantially dopmainergic neurons.

The Tissue Cultures of Luskin and Boss Are Not the Same as Those of the Invention

The neuronal tissue of the invention consists essentially of partially differentiated neuronal progenitor cells that maintain a capacity to undergo mitosis and are capable of differentiating into substantially only dopaminergic neurons. Namely, the invention of the present application includes a new type of cell of a structural and/or chemical composition such that it is sufficiently committed to differentiate along only one pathway, such that the resultant terminally differentiated cells are solely of one type, *i.e.*, dopaminergic neurons. Dec. at ¶ 22. As is explained by the specification, the cells are prepared by transient exposure of pluripotent neuronal progenitor cells (stem cells that retain the structural and/or chemical features that permit them to descend down two or more pathways of differentiation), Dec. at ¶¶ 18 and 19, to certain growth factors such as GNDS, LIS, IL-1, IL-11, and thyroid hormone. *Id.* In preparing the patent application, these specific cells have been referred to as "partially-differentiated

neuronal progenitor cells" or "determined progenitor cells," a new terminology developed by the inventor to convey that the cells still remain capable of expansion at some level of differentiation or commitment to a differentiation pathway had been developed. *Id.* Thus, "partial differentiation" as used in this patent application is meant to express a reduction of pluripotency. *Id.* Thus, the cells of the invention differ from those disclosed in Boss and Luskin in two significant respects. First, as previously discussed, the cells of the invention retain these chemical and/or structural features which allow them to undergo mitosis (continuous self renewal). The cell compositions disclosed in both Boss and Luskin are comprised of cells that do not retain this ability. Additionally, the cells compositions of the invention are structurally and/or chemically incapable of giving rise to more than one tissue type. *See,* Dec. at ¶ 23. They will differentiate into only substantially one specific cell type -- dopaminergic neurons.

Accordingly, for at least these reasons, it is respectfully submitted that the disclosures of Boss and Luskin do not teach all elements of the invention, and therefore to do not anticipate it. Withdrawal of these rejections is respectfully requested.

CONCLUSION

It is submitted that claims 44-49, 51-53, 63, 70-79, 83 and 84 are distinguished over the cited art and are fully compliant with 35 U.S.C. § 112. Reconsideration and allowance of these claims at the earliest opportunity is respectfully requested.

Respectfully submitted,

HORST PESCHEL

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(Date)

KRISTYNE A. BULLOCK
Registration No. 42,371
AKIN GUMP STRAUSS HAUER & FELD LLP
One Commerce Square
2005 Market Street, Suite 2200
Philadelphia, PA 19103-7013
Telephone: 215-965-1200
Direct Dial: 215-965-1348
Facsimile: 215-965-1210
E-Mail: kbullock@akingump.com

KAB:cmb
7186802

Enclosure: Oxford Dictionary of Biochemical and Molecular Biology (1997) at 649
Declaration of Johannes Schwarz